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Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019)

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Abstract

Background: Prostate cancer (PCa) is the second most common disease among men worldwide. It is important to know survival outcomes and prognostic factors for this disease. Recruitment for the largest therapeutic randomised controlled trial in PCa—the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomised Controlled Trial (STAMPEDE)—includes men with newly diagnosed metastatic PCa who are commencing long-term androgen deprivation therapy (ADT); the control arm provides valuable data for a prospective cohort.
Objective: Describe survival outcomes, along with current treatment standards and factors associated with prognosis, to inform future trial design in this patient group.
Design, setting, and participants: STAMPEDE trial control arm comprising men newly diagnosed with M1 disease who were recruited between October 2005 and January 2014.
Outcome measurements and statistical analysis: Overall survival (OS) and failure-free survival (FFS) were reported by primary disease characteristics using Kaplan-Meier methods. Hazard ratios and 95% confidence intervals (CIs) were derived from multivariate Cox models.
Results and limitations: A cohort of 917 men with newly diagnosed M1 disease was recruited to the control arm in the specified interval. Median follow-up was 20 mo. Median age at randomisation was 66 yr (interquartile range [IQR]: 61–71), and median prostate-specific antigen level was 112 ng/ml (IQR: 34–373). Most men (n = 574; 62%) had bone-only metastases, whereas 237 (26%) had both bone and soft tissue metastases; soft tissue metastasis was found mainly in distant lymph nodes. There were 238 deaths, 202 (85%) from PCa. Median FFS was 11 mo; 2-yr FFS was 29% (95% CI, 25–33). Median OS was 42 mo; 2-yr OS was 72% (95% CI, 68–76). Survival time was influenced by

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performance status, age, Gleason score, and metastases distribution. Median survival after FFS event was 22 mo. Trial eligibility criteria meant men were younger and fitter than general PCa population.
Conclusions: Survival remains disappointing in men presenting with M1 disease who are started on only long-term ADT, despite active treatments being available at first failure of ADT. Importantly, men with M1 disease now spend the majority of their remaining life in a state of castration-resistant relapse.
Patient summary: Results from this control arm cohort found survival is relatively short and highly influenced by patient age, fitness, and where prostate cancer has spread in the body.

1. Introduction

The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomised Controlled Trial (STAMPEDE) started recruiting in October 2005. It recruits men with either newly diagnosed metastatic (M1), high-risk localised, or node-positive (N+) prostate cancer (PCa). The trial tests the addition of further treatments to androgen deprivation therapy (ADT), including docetaxel, zoledronic acid, celecoxib, abiraterone, enzalutamide, and (among newly diagnosed M1 patients only) radiotherapy, using a multiarm, multistage design. Research arms have recruited at overlapping times, but the control arm has been consistently ADT alone and recruited throughout [1].

PCa is the second most common cancer worldwide among men. With newer licensed therapies that prolong survival in patients relapsing with metastatic castrate-resistant prostate cancer (mCRPC) [2–9] and the increasingly widespread use of prostate-specific antigen (PSA) testing, men with M1 disease may have lower disease burden at diagnosis than in the past. In this era of PSA testing and effective therapies for patients with mCRPC, there are limited, contemporary, long-term data on the natural history of newly diagnosed patients receiving ADT alone. Data from older studies tend to quote median overall survival (OS) times of 30–36 mo [2,3,10–12] and a median OS of around 18 mo in the castrate-resistant setting. Given recent changes to the management paradigm of mCRPC, it is timely to explore current survival outcomes and treatment standards.

Now the largest therapeutic randomised controlled trial in PCa, the STAMPEDE trial's control arm provides valuable data on survival outcomes, prognostic factors, and subsequent treatments for a prospective cohort of men with newly diagnosed M1 disease receiving standard-of-care therapy. This paper aims to describe survival outcomes for such men and considers these in the context of similar groups in older trials. We also investigate factors associated with prognosis and describe subsequent treatments received following disease progression.

2. Patients and methods

2.1. Overall trial recruitment and eligibility

Patients were recruited to the STAMPEDE trial from >100 sites across the United Kingdom and Switzerland. To be eligible, patients must have PCa that was either high-risk, newly diagnosed, nonmetastatic, node-negative (N0) disease, newly diagnosed M1 or N+ disease, or disease (previously treated with radical surgery and/or radiotherapy) that was rapidly relapsing at the time of randomisation. The patients must have been intended for treatment with long-term ADT started no longer than 12 wk prior to randomisation, if at all. Baseline investigations must have been completed prior to randomisation, including computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis and abdomen, bone scan or equivalent (eg, whole body MRI; chest radiograph, if the chest was not included in the CT scan; or MRI), electrocardiogram, and PSA test. There were no age restrictions, and patients had to be fit for chemotherapy and have no significant cardiovascular history.

2.2. Population of interest

For this prospective cohort analysis, we selected all men with newly diagnosed (within 6 mo prior to randomisation) metastatic PCa who were randomised to the control arm of the STAMPEDE trial between October 2005 and January 2014 (Fig. 1). All patients were planned for treatment with standard-of-care ADT, according to local practice, which comprised

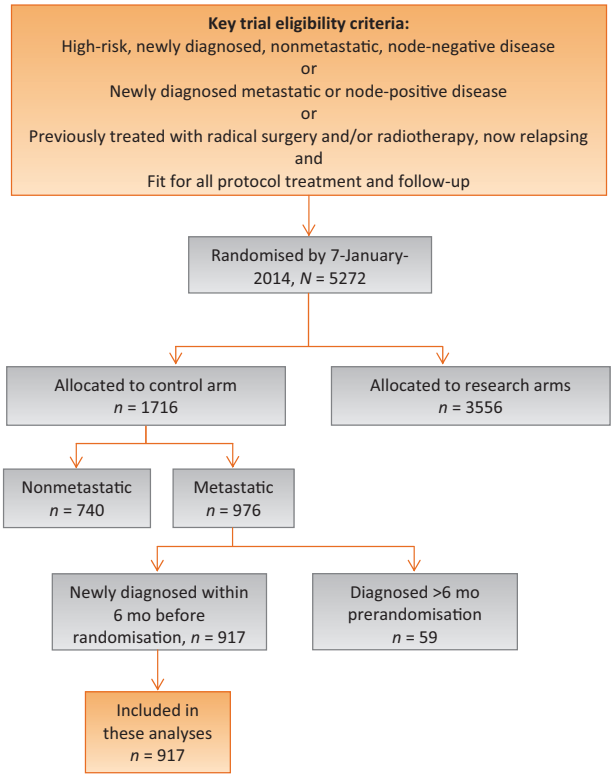

Fig. 1 – Patient selection process for this newly diagnosed M1 control-arm cohort analysis.

either orchidectomy or luteinising hormone-releasing hormone agonists or antagonists, with or without long-term oral antiandrogens. Treatment after disease progression was at the discretion of the consulting clinician.

2.3. Data collection

Baseline data included patient demographics, metastatic sites, regional lymph node status, primary tumour stage, and diagnosis date. Details of disease progression and subsequent treatments were obtained from progression forms. Details of cardiovascular and acute renal events were obtained from follow-up and serious adverse event forms. The protocol can be found online [13]. The trial was registered both on clinicaltrials.gov as NCT00268476 and on controlled-trials.com as ISRCTN78818544, had the relevant regulatory and ethics approval, and all patients gave written, informed consent.

2.4. Outcome measures

The trial's definitive and intermediate primary outcome measures were overall survival (OS) and failure-free survival (FFS) [14]; these outcome measures formed the primary focus of this cohort analysis. Survival was defined as time from randomisation to death from any cause. FFS was defined as time from randomisation to evidence of at least one of the following: biochemical failure; progression either locally, in lymph nodes, or in distant metastases; or death from PCa.

Biochemical failure was defined as failing at diagnosis (PSA nadir >50% of the last pretreatment PSA level), 50% increase above nadir (PSA nadir at least 50% lower than the last pretreatment PSA level but remaining >4 ng/ml), or either a 50% increase from nadir or PSA level >4 ng/ml (PSA nadir <4 ng/ml). The PSA nadir was taken as the lowest PSA value reported in the first 24 wk after randomisation.

Cause of death was determined by blinded central review. Death from PCa was taken when classified by the reviewer as *definitely* or *probably* PCa. The site investigator's determination was used for deaths not yet reviewed.

2.5. Subgroup definitions

Outcomes were defined according to the following baseline groupings: metastases grouping (bone only, soft tissue only, bone and soft tissue); regional lymph node status (N0, N+, NX) and primary tumour stage (≤T2, T3, T4, TX) at baseline; initial Gleason sum score category (≤7, ≥8, unknown); age at randomisation (<60, 60–64, 65–69, ≥70 yr); World Health Organization (WHO) performance status (0 vs 1 and 2); PSA level measured before starting ADT (quintiles) and PSA nadir (<4, ≥4). PSA nadir was only calculable for those patients on trial for at least 26 wk and with at least one documented follow-up PSA value in that time period. Cox model reference groups were as follows: lowest grouping for regional lymph nodes, Gleason score, WHO performance status, and PSA level; soft tissue only for metastases; T3 for primary tumour stage (largest group); and 65–69 yr for age group (contains cohort median age).

2.6. Statistical analyses

Analyses were performed using Stata v13 (StataCorp LP, College Station, TX, USA) using standard survival-analysis methods. Kaplan-Meier estimates were used to produce survival curves. Univariate and multivariate Cox models explored the impact of predefined subgroups. Time-to-event analyses were calculated from randomisation to the outcome of interest, with those not experiencing the event censored at time of last contact, except PSA nadir, which used a landmark at 26 wk postrandomisation to allow for the nadir to be calculated. The impact of PSA nadir could not be examined for men with events or withdrawal of consent prior to 26 wk or insufficient data up to 26 wk. Median follow-up was determined through reverse censoring on death.

3. Results

The cohort selection process is shown in Figure 1. Of 5272 eligible patients randomised to the trial from October 2005 to January 2014, 1716 patients were allocated to the control arm. Of these, 917 men had metastatic PCa newly diagnosed within 6 mo before randomisation. These 917 men form the cohort described here and constitute 17% of patients joining the trial. The data set was frozen in January 2014, with median follow-up of 20 mo (interquartile range [IQR]: 6–37) and total follow-up for all patients of 1449.7 yr.

3.1. Patient cohort

Table 1 shows the cohort baseline characteristics (split by age group in Supplementary Table 1). Median age at randomisation was 66 yr (IQR: 61–71), with 620 of 917 men (68%) <70 yr old. Median time from PCa diagnosis to randomisation

Table 1 – Newly diagnosed M1 control-arm patient characteristics at baseline

Patient level	No.	%
All	917	100
Metastases grouping		
Bone-only	574	62
Soft-tissue * only	106	12
Bone and soft tissue*	237	26
Regional lymph node status		
N0	292	32
N+	545	59
NX	80	9
Bone-only metastases and regional lymph node status grouping		
Bone and N0	276	54
Bone and N+	233	46
Bone and NX	65	NA
Either soft tissue only or bone and soft tissue	343	NA
Primary tumour stage		
≤T2	93	10
T3	515	56
T4	232	25
TX	77	9
Initial Gleason-sum score category		
≤7	156	17
≥8	587	64
Unknown	174	19
Age group, yr		
<60	192	21
60–64	192	21
65–69	236	26
≥70	297	32
WHO performance status†		
0	662	72
1 and 2	255	28
PSA level at randomisation (prehormone therapy), ng/ml (quintile)		
<26.6 (lowest)	184	20
26.9–72.0	183	20
72.3–160.0 (mid)	183	20
164.0–497.0	184	20
≥499.5 (highest)	183	20

PSA = prostate-specific antigen; WHO = World Health Organization.
* Soft tissue included distant lymph node (n = 277), liver (n = 19), and lung (n = 40) metastases.
† WHO performance status is defined as: 0: normal activity without restriction; 1: strenuous activity restricted, can do light work; 2: up and about >50% of waking hours, capable of self-care.

was 2.2 mo (IQR: 1.6–2.9 mo), with a median PSA level of 112 ng/ml (IQR: 34–373 ng/ml) before starting ADT and median time on ADT at randomisation of 46 d (IQR: 24–66 d). Of the 917 men, 906 (99%) reported their current course of ADT as LHRH analogues or antagonists; where type was available, 71% (319 of 449) reported LHRH agonist therapy. The largest proportion of the cohort had bone-only metastases (574 of 917; 62%); 106 of 917 (26%) had both bone and soft tissue metastases; and 106 of 917 (12%) had soft tissue–only metastases. Soft tissue metastasis was overwhelmingly found in distant lymph nodes ($n = 277$; 30%), whereas relatively few men presented with metastases in the liver ($n = 19$; 2%), lung ($n = 40$; 4%), or other sites ($n = 57$; 6%). The low number of patients with visceral metastases made separate analysis impractical. One-third of patients (292 of 917) had no regional lymph node involvement (N0).

3.2. Survival and failure-free survival outcomes

Of the 917 patients, 502 reported at least one FFS event and 238 had died. Median FFS for the cohort was 11.2 mo (IQR: 5.1–28.8 mo) and median OS was 42.1 mo (IQR: 22.7–90.7 mo). Two-year estimates for FFS and survival were 29% (95% CI, 25–33), and 72% (95% CI, 68–76), respectively (Fig. 2).

Tables 2 and 3 show the relative impact of prognostic factors on FFS and OS, respectively. In univariate models, metastases grouping was associated with both FFS and OS, as were primary tumour stage, initial Gleason sum score category, age group, and WHO performance status. Figures 3 and 4 present Kaplan-Meier curves by metastases grouping, WHO performance status, initial Gleason sum score category, and age group, for FFS and OS, respectively. Presence of bone metastases was associated with lower 2-yr OS in men with soft tissue metastases, from 85% to 60% (hazard ratio: 3.42; 95% CI, 1.96–5.97). Higher PSA level before starting ADT and higher primary tumour stage showed evidence of worsened FFS. In the subset of patients with bone-only metastases, there was no evidence that regional lymph node involvement affected either FFS or OS. In the landmark analysis of 457 patients with sufficient follow-up and event free at 26 wk, higher PSA nadir showed evidence of worsened FFS; this was similar for OS in 644 patients with sufficient follow-up and alive at 26 wk.

In multivariate models, presence of bone metastases regardless of soft tissue metastases, worse WHO performance status, higher or unknown initial Gleason sum score category, and younger age at randomisation showed strong evidence of both worsened FFS and OS after adjusting for the other factors. Worsening primary tumour stage and higher PSA level before starting ADT were both associated with poorer FFS outcomes but not OS.

3.3. Cardiovascular and acute renal events

Cardiovascular causes were reported as primary cause of death (COD) for seven patients; none had renal causes reported as primary COD, although it was reported as secondary COD for 11 patients (10 for whom PCa was primary COD). With regard to worse toxicity grade reported up to disease progression, seven patients had G3–4 cardiac disorder and nine patients had G3–4 renal toxicity (Table 4).

3.4. Subsequent treatments and outcomes from progression

Supplementary Figure 1a shows the most frequent series of subsequent therapies reported at progression (given either in combination or independently over time), which were bisphosphonate, chemotherapy, and abiraterone; no further detail is reported here. Supplementary Figure 1b shows time to subsequent therapy from first FFS event; all crossover/subsequent treatments after initial treatment failure were given at the investigator's discretion. Of 502 patients relapsing so far, 50% started chemotherapy within 16 mo

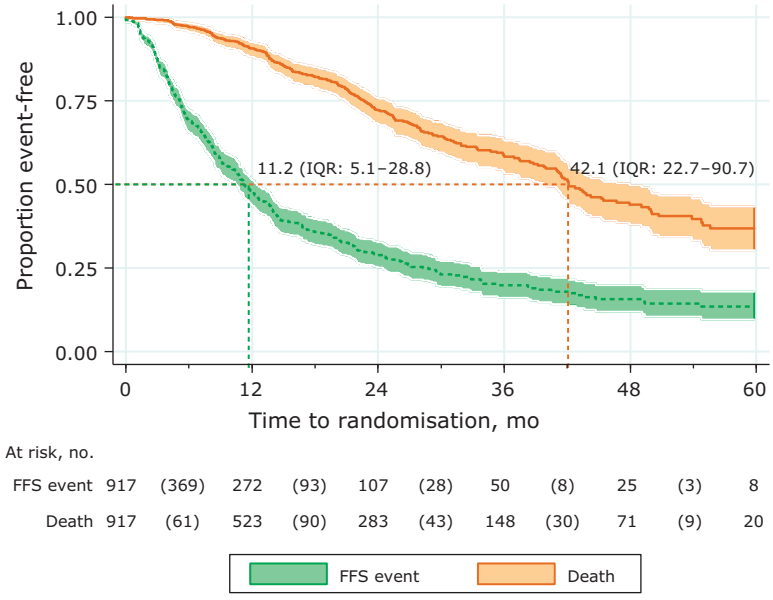

Fig. 2 – Failure-free and overall survival for newly diagnosed M1 patients in the STAMPEDE trial control arm.
FFS = failure-free survival; IQR = interquartile range.

Table 2 – Newly diagnosed M1 control-arm patient characteristics at baseline and failure-free survival prognosis

Patient characteristics			FFS					
No.	%	Patient level	FFS events, no.	2-yr FFS (95% CI)	Univariate HR * (95% CI)	Overall *p* value	Multivariate HR † (95% CI)	Overall *p* value
917	100	All	502	29 (25–33)	–	–	–	–
Metastases grouping								
574	62	Bone only	320	28 (23–33)	2.22 (1.60–3.08)		2.06 (1.45–2.92)	
106	12	Soft tissue only	42	54 (42–65)	1.00		1.00	
237	26	Bone and soft tissue	140	18 (12–26)	2.84 (2.00–4.03)	<0.001	2.41 (1.68–3.46)	<0.001
Regional lymph node status								
292	32	N0	156	31 (24–38)	1.00		1.00	
545	59	N+	295	29 (24–34)	0.93 (0.76–1.13)		0.95 (0.75–1.19)	
80	9	NX	51	21 (12–33)	1.07 (0.77–1.47)	0.5637	0.86 (0.62–1.19)	0.6546
Bone-only metastases and regional lymph node status grouping								
276	54	Bone and N0	150	30 (23–37)	1.00		NA	
233	46	Bone and N+	127	28 (20–35)	0.92 (0.72–1.17)	0.477	NA	NA
65	NA	Bone and NX						
343	NA	Either soft-tissue-only or bone and soft tissue						
Primary tumour stage								
93	10	≤T2	38	52 (39–63)	0.65 (0.47–0.92)		0.65 (0.46–0.92)	
515	56	T3	284	27 (22–32)	1.00		1.00	
232	25	T4	128	27 (19–35)	1.22 (0.99–1.50)		1.14 (0.92–1.42)	
77	9	TX	52	24 (14–36)	1.52 (1.13–2.05)	0.0003	1.10 (0.81–1.51)	0.0262
Initial Gleason-sum score category								
156	17	≤7	74	41 (31v51)	1.00		1.00	
587	64	≥8	344	28 (24–33)	1.55 (1.21–2.00)		1.56 (1.20–2.02)	
174	19	Unknown	84	16 (9–26)	1.92 (1.40–2.64)	0.0002	1.35 (0.96–1.89)	0.0030
Age group, yr								
192	21	<60	137	18 (12–25)	1.53 (1.20–1.95)		1.59 (1.24–2.03)	
192	21	60–64	105	28 (20–36)	1.11 (0.85–1.44)		1.14 (0.88–1.48)	
236	26	65–69	123	32 (24–40)	1.00		1.00	
297	32	≥70	137	36 (29–43)	0.96 (0.75–1.23)	0.0005	0.92 (0.72–1.17)	0.0001
WHO performance status§								
662	72	0	353	31 (27–36)	1.00		1.00	
255	28	1 and 2	149	22 (15–29)	1.51 (1.25–1.83)	<0.001	1.37 (1.12–1.67)	0.002
PSA level at randomisation (prehormone therapy), ng/ml (quintiles)								
184	20	<26.6 (lowest)	73	44 (34–53)	1.00		1.00	
183	20	26.9–72.0	96	33 (24–42)	1.22 (0.90–1.66)		1.26 (0.92–1.71)	
183	20	72.3–160.0 (mid)	101	31 (23–40)	1.37 (1.01–1.85)		1.40 (1.03–1.91)	
184	20	164.0–497.0	121	19 (12–26)	1.88 (1.40–2.52)		1.63 (1.21–2.20)	
183	20	≥499.5 (highest)	111	20 (13–28)	1.99 (1.47–2.68)	<0.001	1.75 (1.27–2.41)	0.0052
PSA nadir #, ng/ml								
357	78	<4	197	46 (40–52)	1.00		NA	
100	22	≥4	72	26 (17– 37)	1.59 (1.21–2.08)	0.001	NA	NA
225	NA	On trial <26 wk						
233	NA	Progressed <26 wk						
2	NA	No follow-up PSA values						

CI = confidence interval; FFS = failure-free survival; HR = hazard ratio; NA = not applicable; PSA = prostate-specific antigen; WHO = World Health Organization.
* Cox models adjusted for age at randomisation as relevant.
† Cox models adjusted for all other variables.
§ WHO performance status is defined as: 0: normal activity without restriction; 1: strenuous activity restricted, can do light work; 2: up and about >50% of waking hours, capable of self-care.
# Analyses for PSA nadir were based on a landmark start time for patients of 6 mo; therefore, 2-yr survival is survival at 18 mo from the landmark.

after an FFS event; other subsequent therapies, including bisphosphonate and abiraterone, were reported starting after a longer time.

Of 502 patients with an FFS event, 230 died; median follow-up time from FFS event was 22 mo. Median survival from FFS event was also 22 mo, with 46% (95% CI, 40–51) alive 2 yr after the first FFS event.

4. Discussion

Within this cohort of metastatic, newly diagnosed PCa patients, treated only with ADT, we found median FFS to be 11.2 mo for the whole cohort from study entry, whereas median OS was 42.1 mo. For FFS and OS, respectively 29% and 72% of patients were event free at 2 yr. Factors prognostic of worsened outcome included presence of bone metastases with or without soft tissue metastases, worse WHO performance status, higher or unknown initial Gleason sum score category, and younger age at randomisation, for both FFS and OS. Worsening primary tumour stage and higher PSA level before starting ADT were associated with worsened FFS only. PSA nadir at 24 wk was pertinent in the landmark analysis of patients who were still responding to ADT at that time. Subsequent therapies reported soonest on disease progression were largely chemotherapy based.

Table 3 – Newly diagnosed M1 control-arm patient characteristics at baseline and overall survival prognosis

Patient characteristics			Overall survival					
No.	%	Patient level	OS events, no.	2-yr OS (95% CI)	Univariate HR* (95% CI)	Overall *p* value	Multivariate HR† (95% CI)	Overall *p* value
917	100	All	238	72 (68–76)	-	–	–	–
Metastases grouping								
574	62	Bone only	146	75 (69–79)	2.22 (1.34–3.69)		2.43 (1.41–4.19)	
106	12	Soft-tissue only	17	85 (73–92)	1.00		1.00	
237	26	Bone and soft tissue	75	60 (51–68)	3.22 (1.89–5.48)	<0.001	3.42 (1.96–5.97)	0.0001
Regional lymph node status								
292	32	N0	70	75 (68–81)	1.00		1.00	
545	59	N+	142	71 (65–76)	1.11 (0.83–1.48)		1.12 (0.80–1.59)	
80	9	NX	26	70 (55–80)	1.17 (0.74–1.84)	0.7280	1.05 (0.66–1.69)	0.8004
Bone-only metastases and regional lymph node status grouping								
276	54	Bone and N0	67	75 (67–81)	1.00		NA	
233	46	Bone and N+	58	74 (65–81)	1.13 (0.79–1.62)	0.492	NA	NA
65	NA	Bone and NX						
343	NA	Either soft tissue only or bone and soft tissue						
Primary tumour stage								
93	10	≤T2	19	75 (61–85)	0.78 (0.48–1.27)		0.81 (0.50–1.33)	
515	56	T3	130	74 (69–79)	1.00		1.00	
232	25	T4	57	69 (59–76)	1.17 (0.85–1.59)		1.17 (0.85–1.61)	
77	9	TX	32	64 (49–76)	1.57 (1.06–2.32)	0.0589	1.16 (0.76–1.79)	0.5126
Initial Gleason-sum score category								
156	17	≤7	36	81 (71–87)	1.00		1.00	
587	64	≥8	159	70 (65–75)	1.60 (1.11–2.31)		1.68 (1.15–2.47)	
174	19	Unknown	43	70 (59–79)	1.84 (1.17–2.88)	0.0178	1.43 (0.86–2.37)	0.0254
Age group, yr								
192	21	<60	78	62 (53–70)	2.07 (1.44–2.99)		2.19 (1.50–3.19)	
192	21	60–64	50	74 (64–81)	1.39 (0.93–2.09)		1.41 (0.94–2.13)	
236	26	65–69	46	74 (65–81)	1.00		1.00	
297	32	≥70	64	79 (71–84)	1.31 (0.90–1.92)	0.0007	1.22 (0.82–1.80)	0.0002
WHO performance status§								
662	72	0	143	79 (75–83)	1.00		1.00	
255	28	1 and 2	95	54 (45–61)	2.39 (1.84–3.10)	<0.001	2.23 (1.70–2.93)	<0.001
PSA level at randomisation (prehormone therapy), ng/ml (quintiles)								
184	20	<26.6 (lowest)	41	74 (63–82)	1.00		1.00	
183	20	26.9–72.0	48	70 (60–78)	0.97 (0.64–1.47)		1.01 (0.66–1.54)	
183	20	72.3–160.0 (mid)	47	76 (66–83)	0.92 (0.60–1.40)		0.88 (0.56–1.36)	
184	20	164.0–497.0	50	74 (65–81)	0.96 (0.63–1.45)		0.70 (0.45–1.09)	
183	20	≥499.5 (highest)	52	67 (57–75)	1.22 (0.80–1.84)	0.6725	0.89 (0.56–1.41)	0.4739
PSA nadir#								
412	64	<4	110	83 (78–86)	1.00		NA	
232	36	≥4	107	59 (52–66)	2.43 (1.85–3.19)	<0.001	NA	NA
250	NA	On trial <26 wk						
20	NA	Died <26 wk						
3	NA	No follow-up PSA values						

CI = confidence interval; HR = hazard ratio; NA = not applicable; OS = overall survival; PSA = prostate-specific antigen; WHO = World Health Organization.

* Cox models adjusted for age at randomisation as relevant.

† Cox models adjusted for all other variables unless marked as NR (not relevant).

§ WHO performance status is defined as: 0: normal activity without restriction; 1: strenuous activity restricted, can do light work; 2: up and about >50% of waking hours, capable of self-care.

Analyses for PSA nadir were based on a landmark start time for patients of 6 mo; therefore, 2-yr survival is survival at 18 mo from the landmark.

These data suggest a relative improvement in survival outcomes compared to older literature, but survival from presentation with M1 PCa remains disappointing (Fig. 2). The median OS reported here is longer than in the Phase III Randomized Double-Blind Study of Clodronate versus Placebo in Patients with Prostate Cancer Metastatic to Bone Who Are Commencing or Responding to Initial Hormone Therapy (MRC PR05; 28 mo) and SWOG Phase III Trial Experience S8894 (33 mo) [11,12,15], shorter than in the control arms of the Androgen-Deprivation Therapy Alone or with Docetaxel in Noncastrate Metastatic Prostate Cancer Trial (GETUG-15; 54 mo) and SWOG Phase III Trial Experience S9346 (49 mo) [12,16], and similar to the 42 mo presented for the control arm in the ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) [17]. Inclusion criteria were not identical for these trials.

Data collected within our cohort allowed examination of prognostic factors at presentation. Of particular interest was the lack of detectable effect of regional lymph node positivity as compared to distant node positivity on overall prognosis. In particular, these data underscore the value of

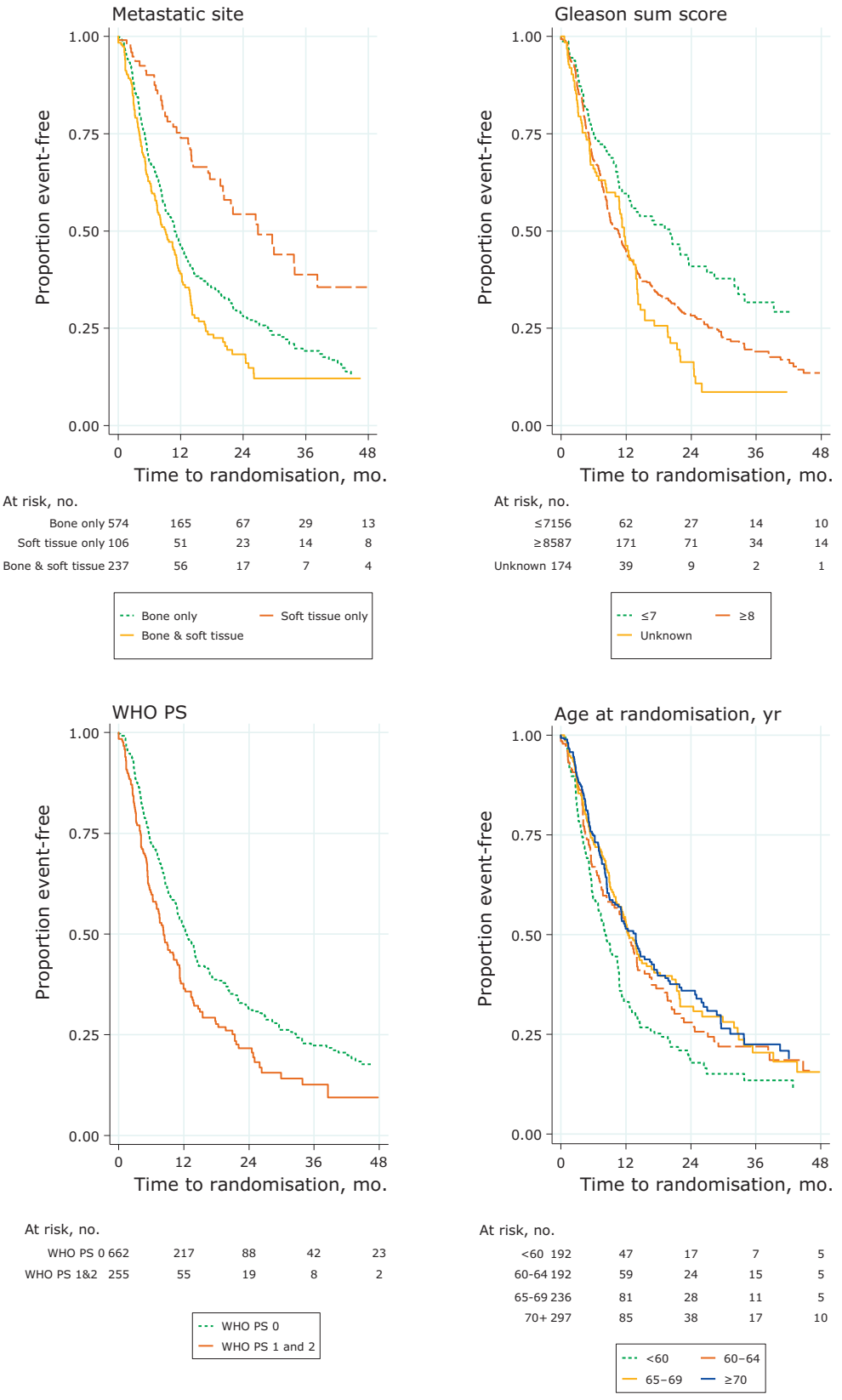

Fig. 3 – Failure-free survival by metastatic site, Gleason-sum score category, World Health Organisation performance status, and age at randomisation. WHO PS = World Health Organization performance status.

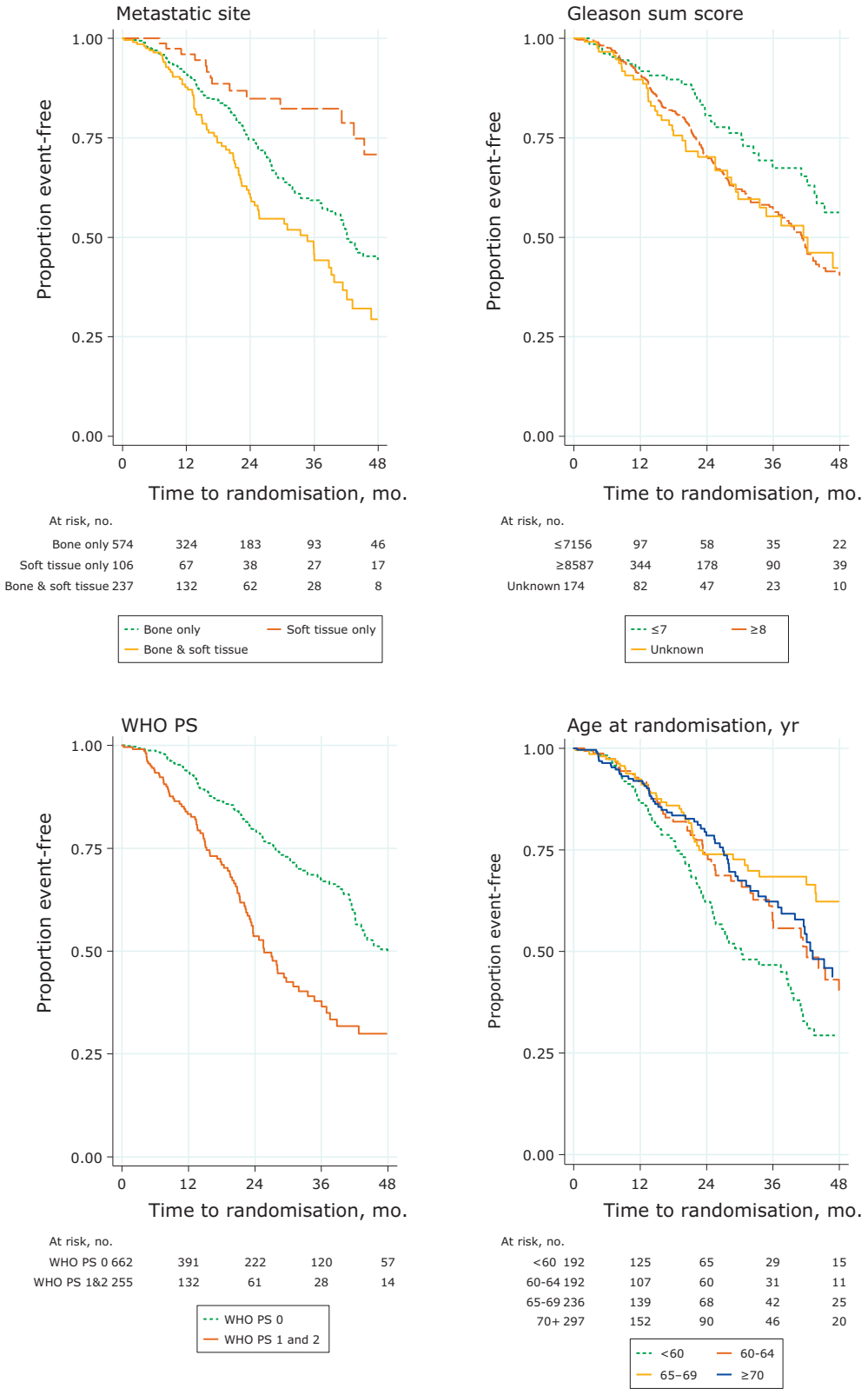

Fig. 4 – Overall survival by metastatic site, Gleason-sum score category, World Health Organization performance status, and age at randomisation. WHO PS = World Health Organization performance status.

Table 4 – Worst reported grade 3–4 cardiac disorder or renal toxicity up to disease progression

	No.	Type of toxicity
Cardiac disorder		
Grade 3	3	1 hypertension, 2 other (1 bradycardia, 1 angina)
Grade 4	4	2 MI, 2 other (aortic stenosis and pulmonary embolism)
Missing	133	NA
Renal		
Grade 3	8	2 renal failure, 1 haematuria, 1 renal impairment, 4 other (3 urinary retention, 1 increased creatinine)
Grade 4	1	1 renal failure
Missing	132	NA

MI = myocardial infarction; NA = not applicable.

soft tissue imaging in patients presenting with a positive bone scan, as concurrent presence of soft tissue metastasis (mainly lymph nodes), in addition to bone metastases, worsened 2-yr OS from 75% to 60%. Although uncommon, soft tissue–only metastases had the most favourable outcome, with 85% 2-yr OS. These effects were similar whether the small proportion with visceral metastases was omitted or included.

The finding that median OS is more than double the median FFS demonstrates that the mCRPC phase now makes up the majority of the survival time rather than being a short terminal phase with limited treatment options. This is consistent with the growing number of available therapies for mCRPC. Indeed, our prospectively collected data were drawn from men treated in the so-called docetaxel era. Several new agents have been licensed for mCRPC since 2002, including therapies such as docetaxel [2,3], cabazitaxel [4], and abiraterone [5,7]; there are other new agents such as enzalutamide [6], radium-223 [8], and sipuleucel-T [9] with positive results but limited availability so far in this cohort. In addition, there have been improvements in supportive care, particularly for men with bony metastatic PCa, with licensing of zoledronic acid [18,19] and denusomab [20,21]. Attitudes in managing men with mCRPC have shifted from care with palliative intent to active treatment using therapies improving survival and reducing morbidity.

The cohort of patients presented here should access these new salvage options. Abiraterone has only been widely available since 2011, with a licence extension to the prechemotherapy population in 2013; hence, we would expect to see changes in patterns of abiraterone use as the data mature. With a similar extension of the licence to pre-docetaxel patients pending for enzalutamide, this use is also likely to change. Likewise, although all patients entering the trial were fit for chemotherapy, the reported median time from relapse to chemotherapy is estimated at 16 mo, with time to the upper quartile not yet reached, suggesting a significant proportion of patients will never receive chemotherapy. As drugs such as abiraterone (also an experimental arm in the main trial) move into wider practice, we shall examine the impact of salvage strategies on OS (Supplementary Fig. 1).

The main strengths of our cohort include patients being from multiple centres with consistent, prospectively collected data and uniform standard-of-care treatment. However, there are limitations. First, our substantive cohort was drawn from the control arm of a clinical trial, inevitably applying eligibility restrictions. This cohort was likely more fit—due to exclusions for cardiovascular disease, men had to be sufficiently fit to potentially receive chemotherapy (to March 2013) and to have no significant cardiovascular history [22] to potentially receive celecoxib (to April 2011 [22,23]—and younger than unselected men with newly diagnosed metastatic PCa (median age was around 10 yr below the median of the PCa population). Use of upfront docetaxel may have deterred older patients from entering the trial and may be one of the explanations for the low median age of this cohort; age is often used inappropriately as a surrogate for fitness. As our cohort may be less likely to die from intercurrent illness, particularly cardiovascular, PCa was the leading cause of death.

Second, our analyses are timed from randomisation rather than diagnosis, making comparability against other cohorts difficult, particularly single-centre series likely to start from diagnosis. Patients were only eligible for STAMPEDE if they were on ADT for no longer than 12 wk before randomisation; most patients had been exposed to 6–8 wk of ADT before randomisation.

Third, median follow-up within this cohort is only 20 mo; recruitment was ongoing when this data set was frozen; however, more than one-half of patients reported a FFS event (502 of 917 men). Fourth, there may be underreporting of treatments used after first progression, particularly for treatments given later in the patient pathway.

The prognostic variables used within the multivariate models were all pre-specified and we feel we used the best disease predictors that we could identify in the data set available. We acknowledge that the multivariate model is likely incomplete. Laboratory values (including haemoglobin, albumin, serum creatinine, and alkaline phosphatase levels) were requested, but the completeness of the necessary data to standardise these variables was lower than we wished to accept and we wanted to avoid imputation of missing values. These are likely important measures, previously identified as prognostic factors in the Halabi nomogram, albeit in CRPC patients [24]. We did not collect data on bone pain [25]. We anticipate that WHO performance status (which we included in our analysis) may already reflect the impact on general health from these other variables.

Although using data from a trial's control arm has limitations, there is a need for a population-based prospective cohort study in this population to address questions prospectively. No such study has been reported, and construction of one would be at great financial cost while taking many years to provide reliable long-term data. The control arm of a high recruiting trial, such as STAMPEDE, therefore provides high-quality prospective data for patients receiving standard-of-care therapy in a hormone-naïve setting. It makes efficient use of the wealth of data collected for the trial, incurring no extensive additional costs and

simultaneously providing treatment safety and efficacy answers. Also, our eligibility criteria were typical of clinical trials in this therapy area, so these data are particularly relevant to planning future studies in this population.

5. Conclusions

Survival outcomes in this large, multicentre cohort of men with metastatic, newly diagnosed disease were shown to have improved compared to previous reports in the literature, although survival still remains disappointing for this patient population. Subsequent therapies primarily consisted of docetaxel alone or with other therapies. Factors independently prognostic of shorter time to both disease progression and death included younger age, presence of bone metastases with or without soft tissue metastases, a Gleason score category $\geq$8, and a WHO performance status worse than zero. It is apparent that survival outcomes in this setting still need to be greatly improved. The STAMPEDE trial will prospectively report on eight treatment combinations randomised against standard of care over 15 yr. Comparative survival results should start to emerge from 2015.

The preliminary results of this study were presented at the American Society of Clinical Oncology annual meeting (ASCO 2013) in Chicago, IL, USA, and the 5th European Multidisciplinary Meeting on Urological Cancers (EMUC 2013) in Marseille, France.

Author contributions: Nicholas David James had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Spears, Sydes, James.
Drafting of the manuscript: James, Spears, Sydes.
Critical revision of the manuscript for important intellectual content: James, Spears, Sydes, Clarke, Dearnaley, De Bono, Gale, Hetherington, Hoskin, Jones, Laing, Lester, McLaren, Parker, Parmar, Ritchie, Russell, Strebel, Thalmann, Mason.
Statistical analysis: Spears.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2014.09.032.

References

[1] Attard G, Sydes MR, Mason MD, et al. Combining enzalutamide with abiraterone, prednisone, and androgen deprivation therapy in the STAMPEDE trial. Eur Urol 2014;66:799–802.
[2] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513–20.
[3] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[4] De Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[5] De Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005.
[6] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[7] Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013;368:138–48.
[8] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369:213–23.
[9] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.
[10] Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. Prostate Cancer Trialists' Collaborative Group. Lancet 1995;346:265–9.
[11] Dearnaley DP, Sydes MR, Mason MD, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst 2003;95:1300–11.
[12] Tangen CM, Hussain MH, Higano CS, et al. Improved overall survival trends of men with newly diagnosed M1 prostate cancer: a SWOG phase III trial experience (S8494, S8894 and S9346). J Urol 2012;188:1164–9.
[13] Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy. About STAMPEDE. STAMPEDE Web site. http://www.stampedetrial.org/.
[14] Parmar MK, Barthel FM, Sydes M, et al. Speeding up the evaluation of new agents in cancer. J Natl Cancer Inst 2008;100:1204–14.
[15] Dearnaley DP, Mason MD, Parmar MK, et al. Adjuvant therapy with oral sodium clodronate in locally advanced and metastatic prostate cancer: long-term overall survival results from the MRC PR04 and PR05 randomised controlled trials. Lancet Oncol 2009;10:872–6.
[16] Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149–58.

[17] Sweeney C, Chen Y-H, Carducci M, et al. CHAARTED: ChemoHormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer [abstract LBA2]. J Clin Oncol 2014;35(suppl).
[18] Saad F, Chen YM, Gleason DM, et al. Continuing benefit of zoledronic acid in preventing skeletal complications in patients with bone metastases. Clin Genitourin Cancer 2007;5:390–6.
[19] Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst 2002;94:1458–68.
[20] Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011;377:813–22.
[21] Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials. Eur Cancer 2012;48:3082–92.
[22] Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.
[23] James ND, Sydes MR, Clarke NW, et al. STAMPEDE: systemic therapy for advancing or metastatic prostate cancer—a multi-arm multi-stage randomised controlled trial. Clin Oncol (R Coll Radiol) 2008;20:577–81.
[24] Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone-refractory metastatic prostate cancer. J Clin Oncol 2003;21:1232–7.
[25] Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group trial 9346 (INT-0162). J Clin Oncol 2006;24:3984–90.